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Metastasis After Primary Treatment — Peri-Operative and Bladder-Preservation Therapy in Muscle Invasive Diseases

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1. Introduction

Bladder cancer is the seventh most prevalent cancer worldwide and the second most common genitourinary malignancy. As such, it is a significant cause of morbidity and mortality. Although 75% of patients present with non-muscle invasive bladder cancer (NMIBC) at initial diagnosis and can be managed with transurethral resection (TUR), the remaining 25% show muscle-invasive bladder cancer (MIBC) at presentation (Messing, et al., 1995). In spite of improvements in surgical technique, survival rates and outcomes for patients with MIBC are not good. Radical cystectomy is unsuccessful in approximately 50% of patients with MIBC, and the 5-year overall survival rate after radical cystectomy for MIBC is only 40%-60% (Ghoneim, et al., 1997; Stein, et al. 2001; Shariat et al., 2006 Koga et al., 2008).

For these reasons, peri-operative therapies, including neo-adjuvant and adjuvant chemotherapy, have become more prominent and have been investigated in many trials and studies (Hussain, et al., 2003; Goethuys and Van Poppel, 2012). Unfortunately, the percentages of patients receiving neo-adjuvant and adjuvant chemotherapy for locally advanced bladder cancer (T2-T4a) are only 12% and 22%, respectively (Feifer et al., 2011). One reason for the low treatment rate with these modalities is that some urologists do not prefer a conservative treatment option or to engage in a surgical approach, while others do not collaborate easily across disciplines. This paper will provide a clear, straightforward description of trends in peri-operative therapy for bladder cancer.

Organ conservation by combined modality therapy is commonplace in contemporary oncology and has achieved success in selected patients with various types of malignancies, such as breast, larynx, esophagus, and prostate. However, radical cystectomy remains the most

commonly offered treatment for bladder cancer; indeed, it is sometimes performed unconditionally, even though this operation holds the possibility of significant morbidity. Modern bladder conservation approaches combine surgery, chemotherapy, and radiation therapy. However, there is variation in each protocol and in the methods used to carry out the protocols.

Over the last decade, numerous investigators have paid special attention to the multiple interacting molecular pathways in urothelial cancer cells, and have demonstrated the complex mechanisms of such interactions and their pathological roles in human bladder cancer. Previous *in vivo* and *in vitro* studies have identified several factors as key to the development and progression of urothelial cancer cells. In this paper, we highlight some of the major molecular pathways and their clinical and pathological significance in bladder cancer. We also present some molecular targeted agents and clinical trials in patients with MIBC.

2. Neo-adjuvant chemotherapy

One advantage of neo-adjuvant therapy compared with adjuvant therapy is that patient tolerance is better; this is because the therapy is administered before surgery, including before radical cystectomy. In addition, neo-adjuvant therapy allows for down-grading and down-staging, which may increase the likelihood of resectability (Calabro and Sternberg, 2009). Studies have shown that preoperative neo-adjuvant chemoradiation therapy reduced tumors to the level of pT0 in approximately one quarter to one third of patients by the time cystectomy was performed (Grossman et al., 2003; Alva et al., 2012). Such statistics give supporting evidence to the possibility that bladder conservation therapy is a practical alternative for selected patients with MIBC. This section will outline the history and present status of neo-adjuvant therapy for patients with MIBC.

There have been several key randomized trials of radical cystectomy alone or with neo-adjuvant therapy (Table 1). Among these trials, there has been no report of any single-agent regimen producing a survival benefit through neo-adjuvant therapy (Wallance et al., 1991; Martinez-Pineiro et al., 1995). A similar result was confirmed in a meta-analysis of individual data from 2688 patients enrolled in 10 randomized trials (Advanced Bladder Cancer (ABC) Meta-analysis Collaboration, 2003). On the other hand, there have been conflicting results on the survival benefit of multi-agent chemotherapy. Among them, the Nordic Cystectomy Trial I, performed using preoperative radiation therapy and 2 cycles of cisplatin (CDDP) and doxorubicin (DXR) for patients with cT1G3-T4NxM0 disease, demonstrated no survival benefit, either 5-year overall or cause-specific (Malmström et al., 1996). Similarly, the Nordic Cystectomy Trial II (3 cycles of CDDP and methotrexate, MTX) showed no overall significant difference in 5-year survival in 317 patients (Sherif et al., 2002). Thus, early trials revealed no significant survival benefit of neo-adjuvant chemotherapy. Interestingly, however, the Nordic Cystectomy Trial I also showed a 15% difference in overall survival for T3–T4a patients ($P = 0.03$). In addition, a combined analysis of the two Nordic Cystectomy Trials showed that the 5-year survival rates of patients receiving neo-adjuvant therapy (56%) were significantly better ($P = 0.049$) compared with the patients not receiving neo-adjuvant therapy (48%) (Sherif, et al.,

2004). These investigators concluded that neo-adjuvant platinum-based combination chemotherapy was associated with a 20% reduction in the relative hazard of the probability of death. In addition, a total of 449 patients from Nordic Cystectomy trial also showed that percentage of pT0N0 was nearly double in the neo-adjuvant arm compared with controls (22.7% versus 12.5%, $P = 0.006$). Furthermore, there is a report that CDDP, MTX, and vinblastine (VBL) showed more favorable results with neo-adjuvant chemotherapy compared with local therapy alone without neo-adjuvant therapy (Medical Research Council, 1999). On the basis of previously reported studies, one opinion is that neo-adjuvant chemotherapy cannot be regarded as standard care (Kaufman et al., 2009). On the other hand, a trial with MVAC (methotrexate, vinblastine, doxorubicin [adriamycin], and cisplatin) therapy showed a trend toward a survival benefit with MVAC, although this difference did not reach the level of significance ($P = 0.06$) (Grossman et al., 2003). Another prospective randomized trial by Griffiths et al. (2011) showed that neo-adjuvant chemotherapy produced a survival benefit. This study had a large impact because of the large study population ($n = 976$) and long follow-up periods (median and interquartile range = 8.0 and 5.7 to 10.2 years). Thus, there are contrary opinions regarding the survival benefit of neo-adjuvant chemotherapy for patients with MIBC. However, a meta-analysis of 11 randomized trials conducted by the Advanced Bladder Cancer Meta-analysis Collaboration that included 3005 bladder cancer patients demonstrated that neo-adjuvant CDDP-based therapy had a significant positive effect on the absolute 5-year overall survival rate ($P = 0.003$) and absolute disease-free survival rate ($P < 0.0001$) compared with local therapy alone. A similar finding was reported in an additional meta-analysis (Winquist et al., 2004).

Authors (year)	Intervention	N	Clinical stage	Comments
Wallace (1991)	CDDP + Radiation therapy Radiation therapy alone	255	T2-4NxM0	No difference for overall survival (odds ratio=1.13 and 95% confidential interval=0.80-1.57)
Martinez (1995)	CDDP+Cystectomy Cystectomy alone	121	T2-4a Nx-2M0	pT0 was found in 14.3% of the experimental arm. No difference for cause-specific survival ($P=0.1349$).
Malmström (1996)	CDDP+ADM+Cystectomy Cystectomy alone	325	T1G3- T4aNxM0	ND for overall survival ($P=0.1$) in T1-2 15% benefit in T3-4a
ICT (1999)	CMV + definitive treatment Definitive treatment alone	976	T2G3- T4aN0/XM0	3-year overall survival rates were 50.0% in chemotherapy arm versus 55.5% in no-chemotherapy arm ($P=0.075$).
Sherif (2002)	CDDP+MTX+Cystectomy Cystectomy alone	317	T2-4a NxM0	pT0 in experimental arm was higher (26.4%) than control arm (11.5%, $P=0.001$). No difference for overall survival
Grossman (2003)	MVAC+Cystectomy Cystectomy alone	317	T2-4a NxM0	Pathological CR was higher in MVAC group ($P<0.001$). Trends in benefit for overall survival ($P=0.06$).
Sherif (2004)	CDDP+ADM or CDDP+MTX +Cystectomy vs Cystectomy	620	T1G3- T4aNxM0	5-year overall survival rate were better ($P=0.045$) in experimental arm (56%) than that in control arm (48%).
ICT (2011)	CMV + definitive treatment Definitive treatment alone	976	T2G3- T4aN0/XM0	5-year overall survival rates were 49 versus 43% and 10-year rates were 36 versus 30% ($P=0.037$).

ICT: International Collaboration of Trialists

Table 1. Randomized studies for Neo-adjuvant therapy

3. Adjuvant therapy

The advantage of adjuvant chemotherapy compared with neo-adjuvant chemotherapy is that various clinical judgments can be made based on complete pathological information. This avoids over-treatment and unnecessary adverse events because pathological staging enables improved accuracy in patient selection for specific therapies. However, the anti-tumor effects and survival benefits of adjuvant chemotherapy are controversial. Several randomized prospective trials showed that adjuvant chemotherapy following cystectomy produced a survival benefit (Skinner, et al., 1991; Stockle 1995). However, these reports are relatively old (1990s) and underpowered (<100 patients). A study in 2010 by Paz et al. showed significantly longer overall survival in patients receiving adjuvant chemotherapy than in patients without adjuvant chemotherapy. Although this study had a relatively large number ($n = 142$), it was closed early because of slow data accrual and un-published data. Other large and recent trials ($n > 100$) have demonstrated that adjuvant chemotherapy following cystectomy did not show a significant survival difference compared with cystectomy alone (Stadler, et al. 2011; Cignetti, et al. 2012). Svatek (2010) conducted a large retrospective study on the relationship between adjuvant therapy and survival, and showed that adjuvant therapy ($n = 932$, 23.6%) was independently associated with favorable overall survival in 3947 bladder cancer patients.

As a result of such controversy, clinical trials on the survival benefit of adjuvant chemotherapy are relatively underpowered because of the small number of patients and are closed early due to poor data accrual. Another reason is the disadvantages of adjuvant chemotherapy, including post-operative complications and decrease in renal function. Donat (2009) found that approximately 30% of patients who received radical cystectomy and were candidates for adjuvant chemotherapy could not receive it within 90 days after operation. Thus, the role and aim of adjuvant chemotherapy after radical cystectomy is not clear. We close our discussion of this issue in the present paper because our main purposes are to discuss the prevention of cancer cell dissemination and understand the processes in MIBC.

4. Bladder conservation strategy

Loss of bladder function is considered a major type of mutilation. Despite advances in neo-bladder construction, a decrease in the quality of life (QOL) is inevitable after cystectomy. In addition, although progress has occurred in peri-operative management, radical cystectomy still has a high risk of complications, including peri-operative mortality (Manoharan, et al., 2009). A recent large review (Shansigh, et al., 2009) of 1,142 patients showed that an early complication (that is, within 90 days) occurred in 64% of patients undergoing radical cystectomy; 13% of the complications were classed as grade 3-5 by the modified Clavien grading system. In recent years, multimodality bladder conservation strategies have gradually gained popularity, and various investigations have been undertaken. In fact, an organ conservation strategy is useful to preserve bladder function and QOL (Zietman, et al., 2003). A modern bladder conservation strategy is the use of trimodality therapy, which combines maximal TUR

followed by an induction course of concurrent radiotherapy and chemotherapy. Patients who incompletely respond to the combined treatment are advised to undergo immediate cystectomy. However, at present, consensus has yet to be reached on the efficacy of bladder conservation therapy for the inhibition of cancer cell progression, and prolongation of survival has yet to be reached (Herr, et al., 1998).

4.1. Present status of bladder conservation therapy

Appropriate candidates for bladder conservation therapy include: patients with T2-4a and clinically node-negative disease, proposed complete or near-complete operation, and adequate organ function to tolerate chemotherapy. Many urologists, medical oncologists, and radiation oncologists have tried various protocols to decrease local recurrence and metastasis, and to improve survival. In the beginning, various monotherapies were also investigated as a safe method of treatment. However, several key studies from pioneer centers in the 1990s to 2000s found that a combination of TUR, chemotherapy, and radiotherapy yielded more favorable outcomes and better anti-tumor effects than monotherapies and other combination therapies (Housset, 1993; Rodel, 2002; Shipley, 2002). At present, trimodality therapy is the major treatment strategy for bladder preservation. In addition, with improvements in radiation therapy and the development of chemotherapy, several trials have been performed in patients with MIBC who are clinically node-positive (Röedel et al., 2002; Gamal El-deen et al., 2009). Furthermore, trials have also been performed in MIBC patients with multiple tumors (Zhang, et al. 2010). Thus, the applications for bladder conservation therapy are expanding. Representative reports on outcomes of bladder preservation therapies are shown in Table 2. This table lists relatively large studies (over 100 patients) on trimodality therapy, as well as randomized trials for patients with MIBC with/without lymph node metastasis. In addition to them, several interesting and important studies have been reported. For example, the protocol that radiation with combination chemotherapy of paclitaxel and CDDP chemotherapy was administrated after TUR was reported in T2-T4a bladder cancer patients. In this protocol, if repeat biopsy showed less than T1 disease, consolidation with similar chemo-radiation therapy was given. If repeat biopsy showed greater than pT1 disease, cystectomy and adjuvant GC therapy were given. Of the 80 eligible patients, 65 patients (81%) were judged complete response. However, of these 65 patients, 8 patients (28%) had local bladder recurrence. At median follow-up of 49.4 months, the actuarial 5-year overall and cause-specific survival rate was 56% and 71%, respectively. In addition, the actuarial rate of surviving with an intact bladder was 59% at 36 months and 47% at 60 months (Kaufman, et al. 2009). On the other hand, On the other hand, most recently, a large study on long-term outcomes of bladder preservation by combined-modality therapy for MIBC has also been reported from Massachusetts General Hospital (Efsthathiou et al., 2012). This study showed the outcomes in 348 patients with T2-4a disease who were treated with CDDP-based chemotherapy and radiotherapy after maximal TUR plus neo-adjuvant or adjuvant therapy. Survival analysis of median follow-up at 7.7 years demonstrated that 5-, 10-, and 15-year overall survival rates were 55%, 35%, and 22%, respectively. On the other hand, the 5-, 10-, and 15-year cumulative bladder-intact disease-specific survival rates were 60%, 45%, and 36%, respectively. These investigators also showed that 102 patients (29%) required follow-up cystectomy. In the conclusion of their report, Efsthathiou et al. stated

their opinion that bladder conservation therapy offers a unique opportunity for urologic surgeons, radiation oncologists, and medical oncologists to work together in a truly multidisciplinary effort for the benefit of patients with invasive bladder cancer. Likewise, we and many other investigators have also suggested that the bladder conservation strategy is a useful and practical alternative for patients who are selected appropriately and when clinical management includes the methods described below.

Author (year)	N	Clinical stage	Random	Operation	Induction therapy	Consolidative therapy	Route	5 years- (%) Survival BIS	
Kachnic (1997)	106	T2-4aNxM0	No	TUR	CMV and RT+CDDP	RT+ CDDP	IV	OS: 52 CSS: 60	43
Shipley (1998)	A: 61 B: 62	T2-4aNxM0	Yes	TUR	A: CMV and RT+CDDP B: No chemotherapy	RT+ CDDP	IV	A: OS: 49 B: OS: 48	A: 38 B: 36
Rödel (2002)	415	T1-4NanyM0	No	TUR	CDDP/CBDCA±5FU+RT or RT alone	–	IV	OS: 50 CSS: 56	42
Eapen (2004)	112	Ta-4N0M0	No	TUR	CDDP+RT	–	IA	OS: 50 CSS: –	– –
Weiss (2007)	112	T1-4N0M0	No	TUR	CDDP+5FU and RT	–	IV	OS: 74 CSS: 82	61
Perdoná (2008)	43 78	T2-4N0M0	No	TUR	CMV and RT CMV and RT+CDDP	–	IV	OS: 60 OS: 72	47 54
Gamal El-Deen (2009)	114 72	T2-4aNanyM0	No	TUR	MCV/MVAC/GC and RT RT alone	–	IV	OS: 60 OS: 68	– –
Zhang (2010)	100	T2-4N0M0	No	Partial	MVAC+RT: as adjuvant for pT3+4 or pN+	–	IV	OS: – CSS: 68	– –
Sabba (2010)	104	T2-3aN0M0	No	TUR	GC and RT+CDDP	–	IV	OS: 55 CSS: –	– –

OS: Overall survival; CSS: Cause-specific survival, BIS: Bladder intact survival

Table 2. Published reports on bladder-conserving therapy (randomized study or patients number >100)

4.2. Intra-arterial chemotherapy in the bladder conservation strategy

Regarding the administration of chemotherapeutic drugs, intravenous infusion has been common in almost all of the large studies (Table 2). On the other hand, intra-arterial chemotherapy has also been used because infusion of chemotherapeutic drug(s) via the intra-arterial route enables a higher drug concentration to be directed at the primary bladder tumor. This treatment strategy, that is, the combination of intra-arterial chemotherapy and radiation therapy, has been used in several studies. For example, Eapen, et al. (1989) reported intra-arterial CDDP and concurrent radiation therapy with/without cystectomy in 25 bladder cancer patients with T3-4N0M0 disease. Another example is that our own study group reported on a combination therapy for 35 bladder cancer patients with T2-4N0M0, for whom two courses of intra-arterial cisplatin and doxorubicin were administered at 3-week intervals, with radiotherapy administered for 4 weeks (Mokarim, et al., 1997). This study showed complete response rates and tumor-free bladder preservation rates of 74% and 54%, respectively. Unfortunately, these reports had relatively small numbers of patients (under 50 patients).

At present, chemoradiation therapy incorporating this infusion protocol has resulted in high complete remission (CR) rates of 83%-93% in patients with locally invasive bladder cancer (Miyanaga, et al., 2000; Eapen, et al., 2004; Hashine et al., 2009). These rates seem to be higher than the CR rates of conventional chemoradiation therapies, although a simple comparison is impossible. However, these studies have also shown 5-year overall survival rates of 50%-66.6% (Miyanaga, et al., 2000; Eapen, et al., 2004; Hashine, et al., 2009), which were similar to the results of other studies using intravenous infusion (Table 2). Problems with this strategy include specific complications (pelvic neuropathy and risk of severe bleeding) and the complexity of the procedure. There has been only one report in a large study population on trimodality bladder preservation incorporating intra-arterial chemotherapy (Eapen, et al., 2004).

With regard to this treatment strategy, there has been a unique and interesting trial (Azuma, et al., 2008) of combined therapy using balloon-occluded arterial infusion of CDDP and hemodialysis with concurrent radiation. In this regimen, the study patients underwent TUR and received balloon-occluded arterial infusion of 100-300 mg CDDP, together with concurrent hemodialysis and a total of 60.4 Gy of radiation. In the first report, this therapy had been administered to 41 patients with T2-4NxM0 disease. All patients with transitional cell carcinoma with T2-3 achieved a complete response (n = 29) and were able to retain their bladders with no evidence of recurrence at a mean follow-up of 132 weeks (Azuma, et al., 2008).

4.3. Partial cystectomy in the bladder conservation strategy

With regard to surgery in bladder conservation therapy, TUR has been used in almost all of the large studies (Table 2). On the other hand, several studies used partial cystectomy as the primary therapy in their treatment strategy (Holzbeierlein et al., 2004; Kassouf et al., 2006; Zhang et al., 2010). As mentioned above, radical cystectomy is the “gold standard” for surgical treatment in patients with MIBC. In contrast, partial cystectomy provides a surgical alternative for selected patients because patients who undergo partial cystectomy are considered to be at higher risk for tumor recurrence and the need for second surgery (Evans and Texter, 1975; Stein et al., 2001). Some authors hold the opinion that partial cystectomy is disproportionately used and that overuse of this operation may constitute inappropriate delivery of health care (Hollenbeck, et al., 2005). For these reasons, partial cystectomy is generally the recommended treatment for adenocarcinoma and/or urothelial carcinoma at the dome of the urinary bladder. However, there is no escaping the fact that partial cystectomy has potential advantages compared with radical cystectomy, for example, functional advantages including continence and sexual function, decreased incidence of surgical morbidity, and avoidance of the need for urinary diversion. In recent years, population-based and matched case-control studies have demonstrated that partial and radical cystectomy provided similar oncologic control and outcome, including metastasis-free and cause-specific survival (Capitanio, et al., 2009; Knoedler, et al., 2012). However, the fact remains that these results are obtained in “selected” patients. In fact, two large cancer centers (Memorial Sloan-Kettering Cancer Center and M.D. Anderson Cancer Center) have suggested that stringent selection of appropriate patients

improves cancer control rates after partial cystectomy for patients with MIBC (Holzbeierlein, et al., 2004; Kassouf, et al., 2006).

Ideal candidates for partial cystectomy are patients with a solitary tumor located in a resectable area not requiring ureteral re-implantation, such as the dome of the urinary bladder, and which can be resected with a 1-2 cm tumor-free margin to preserve normal bladder function. Patients with associated carcinoma in situ should be excluded. Only 3%-10% of MIBC patients who are candidates for cystectomy fit these criteria (Holzbeierlein, et al., 2004; Kassouf, et al., 2006; Capitanio, et al., 2009). Marked variation in outcome after partial cystectomy has been reported: the 5-year recurrence-free survival rates in separate series from M.D. Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center are 39% and 69%, respectively. The bladder conservation strategy of partial cystectomy requires careful attention to patient selection criteria in order to obtain optimal therapeutic outcome.

In recent years, laparoscopy with or without robotic radical cystectomy has begun to be performed; this technique may lead to less bleeding, less post-operative pain, and earlier recovery (Khan, et al., 2012). However, the long-term outcome is unclear, and the operation requires a longer duration and engenders higher cost compared with open surgery. These remain problems to be solved. Likewise, several studies and the experience of several authors with robotic partial cystectomy have been reported (Luchey, et al., 2012; Seyam, et al., 2012). However, almost all of these procedures have been performed on benign tumors including paraganglioma and lymphangioma. On the other hand, there has been a pilot study of robotic partial cystectomy for bladder cancer (Allaparthi, et al., 2010). Similar to radical cystectomy, obstacles to robotic partial cystectomy are high cost, technical difficulties such as decisions regarding tumor margin, and relatively low numbers of ideal patients. The immediate future and further applications of robotic partial cystectomy for bladder cancer are uncertain.

5. GC regimen in peri-operative therapies

For the last several decades, MVAC and CMV (cisplatin, methotrexate, vinblastine) have been especially employed for treating advanced urothelial carcinoma. Additionally, these regimens have been used in almost all of the trials and studies on peri-operative chemotherapy. On the other hand, the GC regimen has been reported as an alternative regimen and more tolerable than the MVAC/CMV regimen in treating advanced urothelial cancer (von der Maase, et al., 2005). In addition to treating advanced disease, the GC regimen seems more advantageous than the MVAC/CMV regimen because the GC regimen has a lower toxicity profile and therefore reduces the potential need for changing the treatment schedule because of toxic side effects. Actually, various studies on peri-operative therapy with GC regimen have been reported. In recent year, a randomized phase III trial of adjuvant GC therapy in 194 patients with pT2G3-pT4N0-2 disease was reported. This manuscript demonstrated that 5-year overall survival rate in adjuvant therapy (43.4%) was similar ($P=0.24$) to that in control (observation and treatment on relapse) (53.7%).

On the other hand, several studies on the local therapeutic effects of neo-adjuvant GC therapy have been published (Table 3). In the series by Dash et al., pT0 was detected in 11 of 42 patients receiving the GC regimen (26%) and in 15 of 54 patients receiving the MVAC regimen (28%). From these results, Dash et al. (2008) concluded that the GC regimen has ability similar to that of the MVAC regimen for inducing pathological down-staging in bladder cancer patients with locally advanced disease. Similar results (showing complete response of MVAC = 31% and GC = 25%) were reported in 2012 by Yeshchina et al. On the other hand, Weight, et al. (2009) reported that the percentages of patients presenting with stage pT0 at the time of definitive surgery who were treated with the neo-adjuvant GC regimen or with cystectomy alone were 10% (2/20) and 9% (8/88), respectively. In recent years, larger studies with a similar design showed that pT0 was detected in 20% (5 of 25) of patients with neo-adjuvant CG and 5% (7 of 135 patients) with cystectomy alone (Scosyrev et al., 2011). These authors concluded that the neo-adjuvant GC regimen was capable of down-staging bladder cancer. Interestingly, Scosyrev et al. also suggested that GC has no effect on disease involving the lymph nodes. Unfortunately, these studies were relatively small series and consisted of patients with a variety of clinicopathological features. Furthermore, the long-term outcome after the GC- and GEM-based regimens for peri-operative treatment is still not fully known. Currently, in clinical practice, including phase II trials, a less toxic GC regimen is commonly substituted for peri-operative MVAC therapy.

Author (year)	N	Clinical stage	Induction	pT0 (%) : P value		Comments
Dash (2008)	A: 42 B: 54	T2-4N0M0	A: GC + cystectomy B: MVAC + cystectomy	26 28	—	No difference in down-staging, disease-free survival, or residual disease. .
Weight (2009)	A: 20 B: 88	T2-4aN0-2M0	A: GC+radical cystectomy B: Radical cystectomy only	10 9	—	This study included 20 patients with GC (PTX in 1) and 9 with other regimens. .
Scosyrev (2012)	A: 25 B: 135	T2-4NanyM0	A: GC+radical cystectomy B: Radical cystectomy only	20 5	P=0.03	Capable of down-staging (proportion of pT0), but no effect on disease in node.
Yeshchina (2012)	A: 16 B: 45	T2-4aN0-2M0	A: GC + radical cystectomy B: MAVC + radical cystectomy	25 31	P=0.645	This choice also affected no significant difference in adjuvant therapy (n=53).

Table 3. Neo-adjuvant gemcitabine plus cisplatin for muscle invasive bladder cancer

6. Molecular-targeted therapy in peri-operative therapy

When molecular targeted therapy is performed, understanding of its clinical significance, pathological roles, and prognostic value is essential. We therefore introduce some molecules that are closely associated with malignant potential and aggressiveness in bladder cancer.

Phase	Intervention	Sponsor	Start year	On going	Identifier : NCT-
0	Lapatinib	University Hospital, Bordeaux	2012	Yes	01245660
I	Intravesical vaccine (rF-GM-CSF, -TRICOM)	University of Medicine and Dentistry of New Jersey	2003	No	00072137
II	IFM, DXR, GEM, CDDP	M.D. Anderson Cancer Center	2001	No	00080795
II	MVAC, bevacizumab	M.D. Anderson Cancer Center	2007	Yes	00506155
II	CBDCA, GEM, ABI-007	University of Michigan	2007	Yes	00585689
II	Dose-dense MVAC	Dana-Farber Cancer Institute	2008	Yes	00808639
II	Erotinib	M.D. Anderson Cancer Center	2008	Yes	00749892
II	Sunitinib after cystectomy following prior neo-adjuvant	University of Michigan	2009	Yes	01042795
II	GEM, CDDP, Sunitinib	MSKCC	2009	Yes	00847015
II	Dose-dense MVAC	Fox Chase Cancer Center	2009	Yes	01031420
II	GEM, CDDP, Sunitinib	Hoosier Oncology Group	2008	No	00859339
II	GEM, CDDP, Sorafenib	Fondazione IRCCS Istituto Nazionale dei tumori	2010	Yes	01222676
II	CDDP, cabazitaxel	United Bistrol Healthcare NHS Trust	2012	Yes	01616875
II	Dose-dense GC	MSKCC	2012	Yes	01589094

Table 4. Clinical trials of neo-adjuvant therapies

6.1. p53

p53 regulates the cell cycle through inhibition of the cell cycle progression at the G1/S transition, and p53 is also involved in various important cellular processes related to angiogenesis, DNA repair, apoptosis, and response to therapy in bladder cancer cells (Mitra, et al., 2006). The first report on the prognostic value of p53 expression in patients with bladder cancer demonstrated that p53 expression status predicted recurrence and survival after radical cystectomy in patients with organ-confined bladder cancer (Esrig, et al., 1994). After that, many investigators showed that p53 mutations occur in approximately 50% of cases of bladder cancer, and that altered p53 status is a useful predictor for cancer cell progression and outcome in bladder cancer patients (Sarkis, et al. 1993; Esrig, et al., 1994; Serth, et al., 1995). However, there was controversial opinion regarding the prognostic value of p53. Actually, a meta-analysis that reviewed 117 studies with 10,026 patients showed that there is insufficient evidence to know whether p53 can serve as a prognostic marker for bladder cancer (Malats, et al., 2005).

Two independent clinical trials regarding p53 gene therapy were performed in a phase I study. A study (SCH 58500) of the safety, feasibility, and biological activity of an adenoviral expression vector encoding wild-type p53 was performed in 12 patients with histologically confirmed

MIBC (Kuball, et al., 2002). In another study, replication-deficient adenoviral vectors bearing the wild-type TP53 gene (Ad5CMV-TP53) were transferred into bladder cancer cells of advanced disease by repeated (28-day cycle) intravesical instillation in 13 patients with locally advanced disease (Pagliaro, et al., 2003). These studies showed that such methods are safe, without no dose-limiting toxicity, and feasible for treatment of patients with bladder cancer. Yet, although the use of gene therapy in combination with transduction-enhancing agents increased transduction efficacy and promoted a high level of patient tolerance, some investigators believe that more improvements in the efficacy of gene transfer and greater knowledge of gene expression levels are required to develop more effective gene therapy.

There is the opinion that locally advanced bladder cancer cells that harbor p53 alterations may respond beneficially to adjuvant chemotherapy containing DNA-damaging agents (Cote, et al., 1997). In addition, there have been several reports that DNA-damaging agents such as CDDP can increase the sensitivity of the bladder cancer cell lines (Lai, et al., 2005; Matsui, et al., 2007). Thus, gene therapy that targets p53 alterations has the possibility of being effective for bladder cancer patients with advanced disease.

6.2. Epidermal Growth Factor Receptor (EGFR)

Among the members of the EGFR family, ErbB1 and ErbB2 (Her2/neu) are the most studied in human cancers. There is general agreement that they are overexpressed in the majority of patients with urothelial cancer of the urinary bladder, including MIBC, and are positively associated with pathological features (Wright, et al., 1991; Korkolopoulou, et al., 1997; Kossouf, et al., 2008). Furthermore, with regard to their predictive value for prognosis and survival, increased expression of these two molecules has been reported to be associated with worse outcome (Korkolopoulou, et al., 1997; Krüger, et al. 2002; Kramer, et al., 2007). In addition, overexpression of EGFR is known to be more common in MIBC (Kassouf, et al., 2008). From these facts, there is a possibility that EGFR-targeted therapies have the potential to improve prognosis and survival in patients with MIBC.

On the other hand, there have been several reports that ErbB2 expression is not correlated with any pathological features, including grade and stage or survival, in bladder cancer patients (Jimenez, et al., 2001; Kassouf, et al., 2007). To explain this discrepancy in the research findings, differences in patient backgrounds and evaluation methods have been suggested. The differing reports show that there is no general agreement about the pathological significance and prognostic role of the EGFR in patients with bladder cancer. Jimenez et al. made the interesting observation that the frequencies of overexpression of ErbB2 in primary tumors and in metastatic tumors were 37% and 63%, respectively (Jimenez, et al., 2001). This finding may suggest that ErbB2 could be an effective therapeutic target for the inhibition of cancer cell progression after treatment of primary tumors.

Gefitinib (brand name, Iressa) is a small molecular EGFR tyrosine kinase inhibitor that selectively inhibits EGFR. Several clinical trials with gefitinib are now in progress. The results of Cancer and Leukemia Group B (CALGB) study number 9012 showed 23 confirmed objective responses (7 complete responses and 16 partial responses) in 54 assessable patients. The median time to progression and overall survival were 7.4 months and 15.1 months, respec-

tively. Based on these results, the authors concluded that outcomes and survivals were not significantly superior to those of previously reported results with GC alone (Philips et al., 2009). However, there is a report that response rate and overall survival after combination therapy with gefitinib and GC were similar to the rates using GC therapy alone in 54 chemotherapy-naïve patients with locally advanced and metastatic urothelial cancer (Philips, et al., 2009).

Cetuximab (Erbix) is an intravenously administered monoclonal antibody against the EGFR. In animal studies, cetuximab showed anti-growth activity against bladder cancer cells (Perrotte, et al., 1999). Furthermore, the combination of paclitaxel and cetuximab exhibited synergistic growth inhibition by suppression of proliferation and enhancement of apoptosis in tumor and endothelial cells in a murine model of metastatic human bladder cancer (Inoue, et al., 2000). Thus, cetuximab is expected to have a remarkable anti-tumor effect in patients with advanced bladder cancer. A study comparing the effects of GC with or without cetuximab in bladder cancer patients with locally advanced or metastatic disease is currently underway in a phase II setting.

Trastuzumab (Herceptin) is a recombinant humanized monoclonal antibody to ErbB2 (HER2). This drug has been reported to be safe and effective in other types of malignancies, especially breast cancer (Burstein, et al., 2003). For treating bladder cancer, a phase II study of the effects of second-line treatment with trastuzumab monotherapy in patients with metastatic urothelial cancer and HER2 overexpression was completed in Germany (protocol number ML17599). In addition, a multicenter phase II trial investigating trastuzumab together with paclitaxel, carboplatin, and gemcitabine was conducted in 57 patients with advanced urothelial cancer having positive expression of ErbB2 as determined by immunohistochemistry (CCUM-9955) (Hussain, et al., 2007). This study showed a 70% response rate, and median times to progression and survival were 9.3 months and 14.1 months, respectively. Interestingly, Trastuzumab is being evaluated in combination with paclitaxel and radiotherapy as a bladder conservation strategy.

Lapatinib is an oral small-molecule dual tyrosine kinase inhibitor of the EGFR and ErbB2. It produces a remarkable response and anti-tumor effect in patients with urothelial cancer. Synergic anti-tumor effects with various chemotherapy regimens are known to occur in urothelial cancer cell lines (McHugh, et al., 2007). This phenomenon may enable reduced-dose chemotherapy and/or reduced toxicity. On the other hand, a phase II study by Wulfing et al. (2005) showed disappointing results in that only 2 out of 59 study patients showed partial response when treated with lapatinib. Further studies and trials are necessary to obtain details with regard to the optimal use and efficacy of lapatinib.

Erlotinib (Tarceva) is an oral small-molecule EGFR tyrosine kinase inhibitor. It has characteristics that inhibit activities of wild-type EGFR and mutant EGFRvIII without decreasing the level of EGFR protein in a reversible manner (Zureikat and McLee, 2008). This agent has been approved for metastatic non-small cell lung cancer and metastatic pancreatic cancer. In bladder cancer, several clinical trials, including a phase II study, are exploring the use of erlotinib as a prevention strategy or as neo-adjuvant therapy (NCT00749892).

6.3. Vasculogenesis-related factors

Bevacizumab (Avastin) is a monoclonal antibody that acts as a VEGF inhibitor. It can bind all VEGF isoforms. Bevacizumab is approved by the FDA for treating various solid tumors, including colorectal cancer, breast cancer, and renal cell carcinoma. In urothelial cancer, a phase II trial is being conducted on the use of cisplatin, gemcitabine and bevacizumab in combination for metastatic urothelial cancer (Cancer: Hoosier Oncology Group, study number GU04-75). A study by Hahn et al. (2011) showed that the best response, according to the Response Evaluation Criteria in Solid Tumors, was complete response in 8 patients (19%) and partial response in 23 patients (53%), out of 43 patients with metastatic or unresectable disease. In addition, it showed that the median progression-free survival was 8.2 months, with a median overall survival time of 19.1 months. Based on these results, these investigators concluded that the full risk and benefit profile of this treatment in patients with metastatic urothelial cancer will be determined by an ongoing phase III trial. In another study, phase II trials are evaluating a neo-adjuvant GC regimen on the use of dose-dense (DD)-MVAC + bevacizumab followed by radical cystectomy in patients with MIBC and patients with resectable urothelial cancer of the bladder (NCT-00506155). An interesting pre-clinical trial involving bevacizumab is being conducted, testing a combination of photodynamic therapy (well-known as an emerging diagnostic and therapeutic strategy in bladder cancer [Patel, et al., 2011]), bevacizumab, and fluorescence confocal endomicroscopy as a promising cancer treatment approach (Bhuvaneswari, et al., 2010). A similar treatment strategy using a combination of photodynamic therapy and molecular targeted therapy is being investigated by another study group using bevacizumab and cetuximab in a murine bladder cancer model (Bhuvaneswari et al., 2011).

Thrombospondin (TSP)-1 is well-known as a representative molecule having anti-angiogenic properties under physiological and pathological conditions. In bladder cancer, TSP-1 expression has been negatively associated with malignant aggressiveness. (Grossfeld, et al., 2003). This report also showed decreased expression of TSP-1 has been observed to predict poor survival in patients with bladder cancer. Interestingly, these investigators also found that alteration of p53 may decrease TSP-1 expression in bladder cancer. From these results, TSP-1 is speculated to be an effective and potential target for novel therapies. Actually, a plan for TSP-1-target therapy has already been in existence and has been investigated in preclinical studies, including a phase I trial (Taraboletti, et al., 2010; Li, et al., 2011). Unfortunately, such a clinical trial is not being conducted in patients with MIBC.

7. Conclusions

In this paper, we described various trials and newly treatment strategies for patients with MIBC. In present, choice of all or a part of operation, chemotherapy, and radiation therapy is major treatment strategy for these patients. In addition, molecular-targeted therapy will be added to these conventional therapies in near future. However, many urologist, medical oncologist, and radiation oncologists have a feeling that the near future strategies may not

adequate to give satisfaction for outcome and survival in MIBC disease. So, numerous investigators keep on studying the pathological features and molecular mechanism of bladder cancer to break through the difficulty of the present strategies. We hope more detailed basic studies and precise clinical trials in bladder cancer.

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